Indian Journal of Gynecologic Oncology (2024) 22:21
https://doi.org/10.1007/s40944-023-00781-x

REVIEW ARTICLE

Time Factor in External Radiotherapy: Radiobiological Mechanisms and Clinical Applications

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Received: 28 June 2023 / Revised: 24 October 2023 / Accepted: 28 November 2023 / Published online: 10 January 2024

Abstract

This review article explores the critical role of time in external radiotherapy, focusing on the concepts of fractionation and spreading. It traces the evolution of radiobiology, highlighting key milestones that have shaped current treatment strategies. The article delves into the four fundamental principles of radiobiology—Repair, Redistribution, Reoxygenation, and Repopulation—and their implications for fractionated radiation therapy. It further discusses the clinical applications of these principles, including hyperfractionated, accelerated, and hypofractionated treatments. This review provides a comprehensive understanding of how the time factor influences the effectiveness of radiotherapy and its impact on healthy and tumor tissues.

Keywords External radiotherapy · Fractionation · Spreading · Radiobiology · Repair of sublethal damage · Redistribution in cell cycle · Reoxygenation · Repopulation · Hyperfractionation · Accelerated treatment · Hypofractionated treatment

Introduction

External radiotherapy is a commonly used treatment modality in the fight against cancer. It involves delivering high-energy ionizing radiation directly to the tumor area, with the aim of destroying cancer cells while preserving the surrounding healthy tissues. The biological effects of radiation are determined by a multitude of factors. Primarily, they depend on the type and physiological state of the irradiated tissue, the nature of the radiation used, as well as the absorbed dose and its distribution in the tissues. However, these effects are also strongly conditioned by the way the dose is distributed over time, that is, by the chronology of the irradiation [1–4].

The "time factor" in external radiotherapy is a crucial element that is mainly divided into two aspects: fractionation

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and spreading. Fractionation refers to the number of fractions and the dose per fraction, while spreading concerns the number of days between the first and last radiotherapy session.

Mastering these factors in radiotherapy is essential for several reasons. It allows for increasing the effectiveness of the treatment at the level of tumor tissues, limiting the consequences of irradiation on healthy tissues, comparing two treatments that differ by several irradiation parameters, and adjusting the dose if a modification of the standard rhythm is necessary. In this article, we will explore the evolution of ideas regarding the time factor in external radiotherapy, the radiobiological mechanisms involved in fractionation and spreading, as well as their clinical applications.

Evolution of Ideas

The journey of radiobiology began in the late nineteenth century and has since evolved significantly, shaping the way we understand and treat various diseases today. This chapter will trace the key milestones in the development of radiobiology, highlighting the significant contributions of various scientists and the impact of their discoveries on the field.

In 1895, Wilhelm Roentgen made a revolutionary discovery that would forever change the course of medical science—the X-rays [5]. This discovery was quickly followed by the identification of radioactivity by Henri Becquerel in 1896 and the isolation of radium by Pierre and Marie Curie in 1898, further expanding our understanding of radioactive elements [6–8].

In 1900, Becquerel conducted the first unintentional radiobiological experiment. He carries a radium tube in his pocket and develops an erythema (a skin redness like a burn) which presents itself 15 days after exposure to radium. This event marked one of the first indications that radiation can cause biological damage. This experiment was voluntarily repeated by Pierre Curie in 1901, confirming the effects of radiation on living tissue and marking the beginning of radiobiology [9].

In the years that followed, X-rays found applications in both diagnostic and therapeutic domains. However, it was the work of Regaud in 1922 that led to a significant shift in the approach to radiation therapy. Regaud demonstrated that fractionated irradiation of a goat's testicle led to sterilization with minimal skin lesions, unlike a single session of irradiation that resulted in severe skin lesions. This differential effect between the testicle and the scrotum skin paved the way for the adoption of a conventional treatment regimen in 1930, involving 20 to 30 sessions over 4 to 6 weeks, with a weekly dose of 5×2 Gy. The adoption of these fractionated regimens was a significant advancement in radiation therapy. It allowed for more effective treatment of cancers, with fewer side effects compared to treatment with single, large doses of radiation [10, 11].

In 1944, Strandqvist conducted the first systematic study of clinical data for his doctoral thesis. His objective was to analyze the variations of the necessary dose for a particular biological reaction (iso-effect dose) when the dose distribution over time was modified. The biological effects studied included skin reactions and the healing of epitheliomas. The study concluded that the tolerance dose for the skin and the dose to sterilize the epithelioma increased with the duration of the treatment and regardless of the spreading, the dose corresponding to the healing of cancer was higher than the dose causing an epidermitis. He found no differential effect, which was different from Regaud's findings. However, the study faced a problem of insufficient number of patients [12, 13].

In 1960, Cohen conducted a similar study to Strandqvist's, but on a large number of patients. He found that the slope for skin tolerance is greater than that for the healing of the epithelioma. Cohen concluded that fractionation-spreading protects healthy skin more than cutaneous epithelioma [14–17]. However, the respective role of the two factors remained unknown until then.

In 1969, Frank Ellis introduced the concept of the Nominal Standard Dose (NSD), a formula that facilitated the adjustment of radiotherapy treatments in clinical practice. Ellis's NSD formula was designed to ensure that three different treatment regimens, each with varying fractionation and spread, would yield the same efficacy in terms of early skin and mucosal reactions. This was a significant development in the field of radiotherapy, as it provided a standardized measure for comparing and adjusting treatments. However, the NSD had its limitations and was applicable only to certain conditions. It requires precise dosage calculations, with even small errors potentially impacting the disease's recurrence rate. The NSD is based on normal connective tissue's radiation tolerance, but it doesn't account for the varying sensitivity of other tissues or individual patient factors. Furthermore, its utility in comparing treatments with different fractionation schedules is limited. Despite these constraints, Ellis's NSD formula represented a significant step forward in the precise application of radiotherapy treatments [18].

Linear-Quadratic (LQ) Model

The linear-quadratic (LQ) model is a widely used radiobiological model in radiotherapy that describes the relationship between radiation dose and its biological effect, which is fundamental in understanding the effects of radiation on tissues and optimizing treatment plans. The LQ model is characterized by two parameters: alpha (α) and beta (β). Alpha represents the linear component of cell kill, while beta

represents the quadratic component. The LQ model can be mathematically expressed as: $S(D) = e^{-(\alpha D - \beta D2)}$ where $S(D)$ is the survival fraction of cells after receiving a dose D, and the values of α and β are tissue or cell line-specific, illustrating the unique radiobiological characteristics of different tissues [2].

The LQ model offers several significant advantages in the realm of radiotherapy. Firstly, it demonstrates remarkable flexibility as it can be applied to a wide range of radiation doses and fractionation schemes. This adaptability is crucial in optimizing treatment plans for various clinical scenarios. Additionally, the LQ model facilitates the prediction of iso-effect doses, allowing the conversion of equivalent radiation doses across different fractionation regimens. Its clinical applicability is of paramount importance, as it guides the development of treatment plans and predicts the radiobiological responses of both tumors and normal tissues, enhancing the precision of radiation therapy.

While the LQ model is a valuable tool, it has certain limitations. Notably, it is highly sensitive to its parameters, α and β. Accurate estimation of these values is essential, and even minor variations can substantially affect the model's predictions. Furthermore, the LQ model is based on an assumption of linearity at low doses, which may not always hold true for all tissues. This assumption can limit its accuracy, particularly in scenarios like high dose hypofractionation, where nonlinear responses may occur. Additionally, it's important to acknowledge that the model may not comprehensively represent the intricate complexities of in vivo responses, particularly in situations where multiple biological factors come into play.

Radiobiological Mechanisms Involved in Fractionation and Spreading

Radiobiology, the study of the action of ionizing radiation on biological tissues, has identified four fundamental principles, often referred to as the "4 R's of Radiobiology": Repair of sublethal damage, Redistribution in the cell cycle, Reoxygenation, and Repopulation. These principles play a crucial role in understanding the effects of radiation therapy, particularly in the context of fractionation and spreading [19, 20].

Repair of Sublethal Cellular Lesions

Radiation exposure can result in three types of cellular lesions: lethal, sublethal, and potentially lethal. Sublethal damage repair is a critical mechanism that comes into play during fractionated radiation therapy. Elkind's experiment in 1959 demonstrated that fractionating a dose into two sessions separated by a few hours resulted in a lower lethality rate than delivering the same total dose in a single fraction [21]. This is attributed to the repair of sublethal lesions during the interval between the two sessions. Further studies on mice irradiated on the intestine showed that the lethal dose 50 (LD50), the dose lethal to 50% of the population increased when the irradiation was delivered in two sessions separated by an hour [22]. This suggests that during fractionated treatment, there is a phenomenon of repair of sublethal cellular lesions, which results in an increase in the survival rate of cells and an increase in the iso-effective dose.

The differential effect associated with fractionation is a critical aspect of radiobiology. When comparing two distinct cellular populations after such treatment, it's often observed that one population exhibits a higher survival rate than the other. This is attributed to the relative protection that fractionation provides for the more resistant population. The small difference in survival curves between the two populations is amplified by fractionation, leading to a differential effect between two populations whose survival curves have different shoulders (β). A reduction in the dose per fraction relatively protects the population with a larger shoulder (greater damage repair), a lower slope of the initial tangent (α), and a smaller α/β ratio. The α/β ratio reflects the sensitivity of tissues to fractionation variations. A low α/β ratio characterizes tissues with a high repair capacity, thus relatively radioresistant, with a high sensitivity to fractionation variations, efficacy, or toxicity of high doses per fraction, and protection by low doses per fraction. A high α/β ratio characterizes tissues with a low repair capacity, thus relatively radiosensitive, with a low sensitivity to fractionation variations [23].

At the level of healthy tissue, the effect of fractionation variation on acute and late reactions is significant. The slope of the iso-effect curves of late effects is more pronounced, and the plateau is reached more quickly (2–2.5 Gy) for early reactions than for late reactions (< 2Gy). This suggests that a more pushed fractionation selectively protects against late reactions compared to early reactions, and for doses < 2 Gy/Fr, there is no gain with respect to tolerance for early reactions, but there is an increase in tolerance for late effects. The differential effect of fractionation between healthy tissue and tumor tissue is also significant. The DNA repair enzyme system of normal cells is more efficient compared to a tumor cell (in most cases), leading to a differential effect. The kinetics of cellular repair also play a crucial role. For example, the DL50 increases when the interval between sessions increases due to more significant repair. It is essential to consider not only the importance of cellular repair but also its kinetics. Repairs for late effects take longer to complete (6–9 h) than repairs for early effects [24].

Finally, the α/β ratio for different types of healthy and tumor tissues encountered in clinical practice varies. For example, tissues with rapid renewal have a high α/β ratio

(10–15 Gy), an acute reaction to irradiation, and are not very sensitive to an increase in the dose/fraction. Tissues with slow renewal have a low α/βratio (1–5 Gy), are very sensitive to high doses/Fr, and have a higher risk of severe late reactions. Most tumors have a high α/β ratio. The linear-quadratic model allows the transition from a non-conventional fractionation to a conventional fractionation and vice versa. The concept of the biologically effective dose (BED) is central to understanding the differential effects of fractionation. The BED is a measure of the biological effectiveness of a given dose of radiation, considering both the total dose and the dose per fraction. It is calculated using the linear-quadratic model, which describes the relationship between the dose of radiation and the biological response it induces [24, 25].

Redistribution in the Cell Cycle

The concept of cellular redistribution plays a crucial role in the effectiveness of fractionated radiation therapy. Cellular radiosensitivity varies throughout the cell cycle, with cells being most sensitive in the G2 and M phases and most resistant in the late S phase. Fractionated radiation therapy can exploit this differential sensitivity by allowing cells to redistribute within the cell cycle, thereby increasing the proportion of cells in sensitive phases during subsequent radiation exposures [26–28].

Post-irradiation, cells often experience a temporary blockage, accumulating in the G2-M phase, a phenomenon known as synchronization. As cells progress through the cell cycle, they move from more resistant phases to more sensitive phases. The redistribution of cells within the cell cycle helps maintain the tumor at a certain level of radiosensitivity. This is crucial for the effectiveness of fractionated radiation therapy as it ensures that a significant proportion of tumor cells are in a radiosensitive phase during each radiation exposure. This process, combined with the other factors such as repair of sublethal damage, reoxygenation, and repopulation, contributes to the overall success of fractionated radiation therapy in controlling tumor growth.

Reoxygenation

Reoxygenation is a crucial factor in the effectiveness of fractionated radiation therapy. Oxygen is a potent radiosensitizer, enhancing the effects of radiation. Hypoxic tumor cells, which are often resistant to radiation, can reoxygenate between fractionated radiation exposures, thereby increasing their radiosensitivity. The process of reoxygenation works in a cycle. After a fractionated radiation treatment, the oxygenated cells are destroyed, leaving behind the hypoxic cells. These hypoxic cells then move closer to the blood vessels and reoxygenate, making them more susceptible to the next round of radiation therapy. This cycle of destruction and reoxygenation continues throughout the course of the treatment, maintaining a certain level of radiosensitivity within the tumor [29–31].

Repopulation

Repopulation refers to the proliferation of cells between radiotherapy sessions. This phenomenon is beneficial when it involves healthy cells, as it helps limit the toxic effects on healthy tissues. However, it becomes adverse when it involves tumors, most of which proliferate rapidly. This is a crucial element in the occurrence of acute complications in radiotherapy. The spreading effect, on the other hand, facilitates repopulation. It refers to the distribution of radiation doses over a period, which allows for the recovery and regeneration of cells between sessions [19].

Healthy tissues can be categorized into non-compartmental tissues, which have slow renewal and low mitotic activity, and compartmental tissues, characterized by continuous and rapid renewal due to the controlled multiplication of stem cells. The role of spreading is minimal in non-compartmental tissues as there is little or no proliferation. However, it is significant in compartmental tissues like skin, mucous membranes, intestines, and hematopoietic marrow. Spreading reduces acute effects and improves tolerance in tissues with high mitotic activity if this process is prolonged, but it can cause significant acute effects if the spreading is short.

The effects of overall treatment time and treatment gaps on tumor control probability are pivotal considerations in the realm of radiotherapy, and they demand a comprehensive understanding. Tumor tissues, characterized by a growing cellular population and infinite proliferation of clonogenic cells, show significant repopulation, especially in rapidly growing tumors. During irradiation, repopulation accelerates, with the timing of this acceleration varying among different tumors. To maintain the same probability of sterilization, the total dose needs to be increased if the overall treatment time is extended. For example, the additional dose per additional day of spreading for tumors of the upper aerodigestive tract is 0.6 Gy [32, 33]. Gaps in treatment, whether due to technical issues or patient-related factors, can also negatively impact tumor control probability. These gaps allow tumor cells to recover and can reduce the effectiveness of radiation, so minimizing these gaps is critical for optimal outcomes.

Different tissues and tumor types may respond differently to changes in treatment time and gaps, so treatment planning should be tailored to the specific clinical scenario and radiobiological characteristics of the tissue in question. The differential effect of repopulation depends on the mitotic activity of the compared tissues. Compared to a reference spread (5×2 Gy/week), shortening the overall treatment

time is advantageous in the treatment of tumors with a short potential doubling time (e.g., lymphoma, embryonic tumors, etc.). In such cases, curtailing the treatment period helps mitigate the effects of repopulation. Conversely, extending the overall treatment time for tumors with a long potential doubling time (e.g., adenocarcinomas) may improve early tolerance, but without any impact on sterilization [34].

Clinical Applications

Hyperfractionation and Acceleration

Hyperfractionation and acceleration are two strategies used in radiotherapy to improve the effectiveness of treatment and minimize damage to normal tissues. Depending on the total dose and degree of acceleration, treatments can be classified into hyperfractionated, moderately accelerated hyperfractionated, highly accelerated hyperfractionated, and accelerated treatments. Each of these has specific characteristics in terms of total dose and treatment duration [35].

Hyperfractionated Treatment

Hyperfractionation is supported by radiobiological principles that stem from the delicate balance between delivering smaller radiation doses per fraction (typically less than 1.8 Gy) while increasing the frequency of fractions per day (typically 2–3 fractions). This approach has been shown to confer an unequivocal benefit in the treatment of head and neck cancer, improving both local control and survival without a significant increase in late sequelae. For instance, the EORTC 22791 study on oropharynx carcinoma compared a conventional treatment of 70 Gy in 35 fractions over 7 weeks (2 Gy per fraction) against a hyperfractionated regimen of 80.5 Gy in 70 fractions over the same period (2 fractions of 1.5 Gy per day, with a 4–6-h interval). The 5-year results showed an increase in locoregional control rate from 40 to 59% ($p = 0.02$) with the hyperfractionated treatment, with severe mucosal reactions but no difference in late complications [36].

Moderately Accelerated Hyperfractionated Treatment

Moderately accelerated hyperfractionated treatment involves a similar total dose with shorter spread than conventional treatment. Radiobiologically, this approach reflects the fundamental concept of optimizing the therapeutic index, which is the ratio between tumor control and normal tissue toxicity. The shortened treatment duration is designed to increase the biologically effective dose delivered to the tumor while minimizing the opportunity for cellular repair mechanisms to counteract radiation damage. This approach has been tested in several randomized studies, including the EORTC 22851 study on head and neck cancer, which compared a conventional treatment of 70 Gy in 35 fractions over 7 weeks (2 Gy per fraction) against a moderately accelerated hyperfractionated regimen of 72 Gy in 45 fractions over 5 weeks (3 fractions of 1.6 Gy per day, with a 4-h interval). The results showed improved local control but increased acute and late toxicity [37].

Highly Accelerated Hyperfractionated Treatment

Highly accelerated hyperfractionated treatment involves a reduced total dose and a significantly reduced duration. Radiobiologically, by extremely reducing the overall treatment duration, this approach aims to hinder the normal tissue's ability to repair itself between fractions, thereby increasing the effective biological dose delivered to the tumor, and despite delivering a reduced total dose, this regimen aims also to maintain tumor control by maximizing the biological impact of each fraction. Several randomized studies have tested this approach, including the CHART study on head and neck cancer, which compared a conventional treatment of 66 Gy in 33 fractions over 6.5 weeks (2 Gy per fraction) against a highly accelerated hyperfractionated regimen of 54 Gy in 36 fractions over 12 days (3 fractions of 1.5 Gy per day, with a 6-h interval). The results showed identical tumor control and survival, with more pronounced mucositis but decreased late normal tissue damage [38].

Accelerated Treatment

Accelerated treatment involves delivering a similar total dose of radiation over a shorter period than conventional treatment, typically more than 10 Gy per week. The aim of this approach is to reduce the overall treatment time, thereby minimizing the opportunity for tumor cells to proliferate during treatment, leading to maximize the biological effect of each radiation fraction. However, caution is needed with this approach as it can lead to severe and prolonged acute reactions, as well as early necrosis in some cases. An example of this approach is the CAIR (continuous accelerated irradiation) study on head and neck cancer, which compared a conventional treatment of 66–72 Gy in 35 fractions over 7 weeks (2 Gy per fraction, 5 fractions per week) against an accelerated regimen of the same total dose in 35 fractions over 5 weeks (7 fractions per week). The 3-year results showed improved local control (82% vs 37%, $p = 0.0001$) and overall survival (78% vs 32%), but severe and prolonged mucosal reactions were observed [39].

Hypofractionated Treatment

Hypofractionated treatment involves delivering radiation in larger doses (> 2 Gy per fraction). This approach is particularly beneficial in palliative care settings, where the goal is to alleviate symptoms and improve the quality of life for patients with advanced or incurable cancers. Hypofractionated treatment is also commonly employed for specific types of tumors, including melanoma and adenocarcinomas of the breast and prostate. These cancers have been shown to respond favorably to larger radiation doses per session. The advantage of this approach lies in its potential to reduce the total number of treatment sessions required, thereby offering patients a more convenient and less time-consuming treatment schedule. However, careful consideration must be given to the balance between achieving effective tumor control and minimizing the risk of damage to surrounding healthy tissues [40–44].

Conclusion

The "time factor" in external radiotherapy, which includes fractionation and spreading, plays a crucial role in optimizing treatment effectiveness and preserving healthy tissues. The evolution of radiobiology, from the discovery of X-rays to the development of various treatment strategies such as hyperfractionation and acceleration, has significantly shaped our understanding of radiation therapy. The principles of repair of sublethal damage, redistribution in the cell cycle, reoxygenation, and repopulation underscore the importance of these strategies in enhancing the therapeutic ratio of radiotherapy.

Author Contributions AM and HS performed the literature review, wrote the manuscript, and approved the final version. EM, MH, MB, NZ, AB, IL, KA, ME, and KH all revised the manuscript and approved the final version.

Declarations

Conflict of interest The authors declare that they have no competing interests.

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